

AMENDMENTS TO THE SPECIFICATION

Please amend the paragraph beginning at page 1, line 25 as follows:

As a typical biosensor chip having this kind of surface, BIACORE® which is commercially available from Amersham Pharmacia Biotech., Inc. can be named, which is provided in form of a chip in which a translucent matrix of dextran with carboxylated ends is immobilized on a thin gold film. A patent which is considered to claim such a detection surface is Japanese Patent No. 2815120 (corresponding to [[EP]] U. S. Patent No. 5,242,828 and EP 0 589 867B1) Gazette. This Official Gazette describes a surface formed by the steps of linking organic molecules expressed by a formula HS-R-Y (wherein R stands for a hydrocarbon chain having a chain length exceeding ten atoms and which may be interrupted with hetero atom(s), and Y stands for a ligand or an active group for covalently bonding a biocompatible porous matrix thereto) onto a membrane surface of the ~~free~~ free-electron metal such as gold, silver or the like via the thiol (or mercapto) groups therein, whereby covering said surface with a close-packed monolayer of said organic molecules, and thereafter covalently bonding to the surface a hydrogel as said biocompatible porous matrix, said hydrogel comprising agarose, dextran, polyethylene glycol and the like which may have functional group(s) for linking the ligand.

Please amend the paragraph beginning at page 3, line 18 as follows:

Among the foregoing prior art documents, Japanese Patent No. 2815120 discloses that a monolayer surface in which organic molecules are densely packed can be obtained by chemical adsorption of an organic compound whose chain (R) length exceeds 10 atoms, preferably 12 - 30 atoms, e.g., 16-mercaptohexadecanol having hydrophobic, considerably large alkylene chain, onto a metal surface via thiol group. So obtained monolayer exhibits storage stability, and the patent furthermore suggests it also can be an effective barrier layer to protect the metal surface from chemical corrosion. Onto such a barrier layer a hydrogel which minimizes protein compatibility and non-specific interaction is bound. Hence aforesaid BIACORE® (carrying ~~hydroxygel~~ hydrogel of dextran) which likely is a preferred embodiment of said patented invention has been reduced to practice. It is, however, by no means easy to have the barrier layer uniformly carry the ~~hydroxygel~~

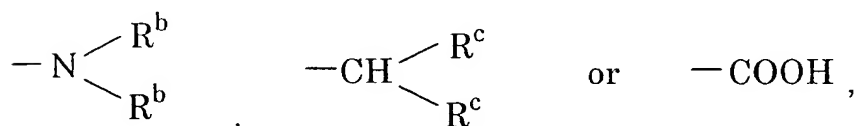
hydrogel and precise operations are required. Also although non-specific adsorption of protein is considerably reduced, there is still room for further improvement.

Please amend the paragraph beginning at page 4, line 14 as follows:

Bavey Pavey et al. adheres said triblock copolymers onto a metal surface via their hydrophobic blocks, i.e., poly(propylene oxide) domain, and it is difficult to obtain a surface with stability, uniformity and reproducibility, like ordinary polymer coating (cf. U. S. Patent No. 4,415,666). Moreover, it is also difficult to raise density of poly-(ethylene oxide) chains.

Please amend the paragraph beginning at page 10, line 10 as follows:

X stands for hydrogen, a functional group or a protected functional group, which functional group may be any which is capable of covalently bonding with said ligand. Taking a case, for example, wherein the ligand is a protein or nucleotide, the functional group or protected functional group may be



wherein R^b each independently stands for hydrogen or $\text{C}_1\text{-C}_6$ alkyl, R^c each independently stands for $\text{C}_1\text{-C}_6$ alkyloxy (ketal or acetal), or the two R^c s may together stand for an oxy (in which case the group as a whole becomes an aldehyde or formyl group: $-\text{CHO}$), or R^c may be an optionally $\text{C}_1\text{-C}_6$ alkyl-substituted ethylene 1,2-dioxyethylene (forming a cyclic ketal). In particular, aldehyde (or formyl) group or protected aldehyde (or formyl) group (ketal group) can be conveniently used. $\text{C}_1\text{-C}_6$ alkyl specifically are methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, n-hexyl and the like, methyl being preferred. Typical preparation processes which are described in said ~~WO 4/86304~~ 01/86301 are illustrated by the following reaction schemes.

Please amend the paragraph beginning at page 15, line 5 as follows:

The surfaces following the present invention which are either subjected to plural times' polymer-linking treatments using solutions containing polymers of the general formula (Ia) or (Ib), or to a linking treatment using a solution containing at least two polymers differing in their ethylene oxide unit (average value) number, have significantly increased amount of linked polymer(s) compared to that resulting from such a treatment given single time, notwithstanding the fact that said single linking treatment with substantially identical polymer(s) brings about fixed, approximately-saturated ~~a-fixed saturated~~ linkage group. Where a polymer of the general formula (Ia) is used, the polymer is dissolved in a suitably buffered aqueous solution, and the solution is contacted with the support surface at an adequate temperature, e.g., ambient temperature, (20-37°C). Depending on the molecular weight of the polymer used, the optimum polymer concentration in the solution varies, while normally a concentration of 0.1 - 5 mg/ml, preferably 1 mg/ml is selected. The contact is carried out by contacting such a polymer solution with the support surface and incubating for several tens minutes to several hours.

Please amend the paragraph beginning at page 15, line 23 as follows:

Thus a fixed amount of the polymer is linked (presumably by chemical bonding) to the support surface. Unlinked polymer is removed from the surface by washing. Any washing liquid can be used so long as it can effectively remove the unlinked polymer, while use of diluted NaOH aqueous solution is preferred. After completion of the washing, the surface is subjected to another polymer-linking treatment using a polymer solution anew. This second linking treatment may be substantially identical with the first linking treatment including the washing. Preferably, the second linking treatment and washing are repeated at least one more time. The polymer used in the second and subsequent linking treatments may be the same to that used in the first treatment, or may have in each time a different poly(ethylene oxide) block molecular weight from that of the polymer used in the first treatment. Where their molecular weights are different, preferably the molecular weight of the polymer used in the second treatment is less than that of the first used polymer. The molecular weight of the polymer may be gradually

reduced as the linking treatment is repeated. Although not in limitative sense, preferred combination of polymers used in the first linking treatment and the second and subsequent linking treatments, based on the molecular weight of the poly(ethylene oxide) block, comprises using a polymer of the general formula (I) or (Ia) having an integer n , as an average value, of 50 - 10,000 in the first linking treatment, and using a polymer having an ethylene oxide unit number less than that of the first used polymer by at least 10, preferably at least 50. Whereby a surface carrying at least $0.1/\text{nm}^2$ of the polymer chain, as converted from data obtained by thermogravimetric analysis of the same surface (cf. for example, W. P. Wuelfing et al., J. Am. Chem. Soc., 1998, 120, 12696 - 12697) is conveniently obtained.

Please amend the paragraph beginning at page 27, line 4 as follows:

A 1 mg/ml acetal-PEG-SH ([Mw] $M_n=5000$) solution in 1M-NaCl-containing 50 mM PBS (pH 7.4) was dropwisely applied to a gold substrate, followed by 30 minutes' standing at room temperature. Then the substrate was washed with 1M NaCl-containing 50 mM PBS (pH 7.4), dropwisely applied with 50 mM NaOH solution, allowed to stand for 30 seconds, and washed three times with 1M NaCl-containing 50 mM PBS (pH 7.4). The whole cycle of above treatments was repeated once again. Thereafter 1 mg/ml MeO-PEG-SH (methoxy-terminated PEG instead of acetal terminals; having no reactivity) ([Mw] $M_n=2000$) solution in 1 M NaCl-containing 50 mM PBS (pH 7.4) was dropwisely applied onto the substrate on which PEG 5000 was immobilized twice, followed by 30 minutes' standing at room temperature. Then the substrate was washed with 1 M NaCl-containing 50 mM PBS (pH 7.4). Onto the so washed surface 50 mM NaOH was dropwisely applied, allowed to stand for 30 seconds, and washed with 1 M NaCl-containing 50 mM PBS (pH 7.4) three times. The whole cycle of the above procedures was repeated twice. Thus a PEG 5000 (2) + PEG 2000 (3)-modified substrate was prepared.

Please amend the paragraph beginning at page 29, line 18 as follows:

Streptavidin-recognizing ability of a composite surface constructed of acetal-PEG-SH ([Mw] $M_n=5000$ and 2000) was investigated, in which PG 5000 and 2000 (2) (2:2)

surface formed by simultaneously introducing PEG 5000 and PEG 2000 onto a gold surface was used.